January 23, 2012

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 7484-review.doc).

Title: Risk factors and therapeutic results of early local recurrence after TACE

Author: Woo Sun Rou, Byung Seok Lee, Hee Seok Moon, Eaum Seok Lee, Seok Hyun Kim, Heon Young Lee

Name of Journal: *World Journal of Gastroenterology*

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Thank you for reviewing carefully and detailedly. By revising according to the suggestions of reviewers, I think my manuscript is improved better than before.

The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer
(We checked the revisions with blue color in the article)

(1) *Reviewed by 01798570*

1) "The specific objectives of this study need to be clarified in the Introduction, and given a clearly explanations."

→ We summarized and clarified the aims of our study.

→ This sentence change to "Therefore, this study aimed to assess the risk factors and survival outcomes of early local recurrence after TACE and investigate the treatment methods for local recurrence and its therapeutic results."

2) "The investigators never specified the study designs used to answer their two main objectives. A clear delineation of the study designs used will provide clarity to the methods. Second, the investigators should describe the inclusion/exclusion criteria for the present study, and explain how 97 patients was excluded. The specific inclusion/exclusion criteria for 134 patients needs to be stated. It would also be helpful to provide a rational for future analysis."

→ We are grateful for the comment. We have added a flowchart as well as the inclusion/exclusion criteria.

→ We excluded the 97 patients because they had not achieved to CR. Because We aimed to investigate local recurrence about only the patients who CR was achieved. We describe the reasons in Figure 1. We did not exclude such criteria as child C, portal vein thrombosis, thrombocytopenia and bilirubin unlike previous studies with the intent of investigating the effects of liver functions or portal vein thrombosis about local recurrence and the frequency of adverse effects in all patients. But, we excluded those who were receiving treatments for untreated concurrent cancers and those whose treatments were delayed for more than 3 months. In accordance with the reviewer's advice, we have clarified the criteria for patients and plotted on a flowchart the process of selecting the enrolled patients to help authors understand better.

3) "The authors simply state they evaluated complete response(CR) based on the 2010 modified Response Evaluation Criteria in Solid Tumors for hepatic target lesions, do not describe the main points of evaluated criteria of CR. The evaluated criteria of CR must illustrate in Material and Method. Although the authors reference the 2010 recommendations, this is not helpful because readers might not be familiar with these recommendations or might use different diagnostic criteria."

→ We described in more detail on "Definition of CR, Materials and Methods"

4) "it would have been valuable to consider including other clinical variables and laboratory data that could predict early local recurrence, such as ascites, portal vein invasion."

→ The results of analyzing "Ascites(Odd ratio: 0.792, P value 0.564), bilirubin and albumin" showed insignificant. Table 2 included the variable "bilirubin, albumin" We analyzed other clinical variable and laboratory data(ex. History of encephalopathy, prothrombin time, LDH, r-GT, presence of LC, child score, ICG test etc.) but could not found significance. We would like to add more variables, but could not described because we had quite a few variables in Table 2 for univariate analysis. It seems that not local recurrence but intrahepatic distant recurrence is associated with such factors for liver function tests as ascites, bilirubin and albumin. We could not find previous articles reporting significant results regarding local recurrence.

→ The present study analyzed the relation between PVT and local recurrence and gained significant results in a univariate chi-square test. However, Early local recurrence occurred in all eight patients with PVT in this study, OR and multivariate analyses could not be performed because none of the patients with PVT at diagnosis exhibited no local recurrence after achieving a CR., which is inserted in the "Results" section and further described in the "Discussion" section.

5) "some language corrections before being published."

→ We edited our manuscript with a copyediting service provided by professional English language editing companies(Certificated Verification Key : 5E26-2162-0A55-612E-6D35)(American Journal Experts: http://www.aje.com). We upload this "Editorial certificate" with revised file.

6) "Results(Table 3, line 6): The type and calculated methods of visual analogue scale(VAS) was used should describe in Material and Method."

→ We have moved the location to the part defining the complication in the "Material and Method" section and described the test method of VAS.

(2) ***Reviewed by 01799566***

1) "Authors should explained that why TACE was the initial treatment modality of all subjects. Are liver transplantation and RF treatment options for these patients. What are the criterias for this issue."

→ We are grateful for the comment. We have elucidated the treatment strategies for patients diagnosed with HCC in the "Subjects" part, and added Figure 1outlining how the enrolled patients were included.

[When curative treatments (liver transplantation, resection, RFA) were difficult due to tumor characteristics, indocyanine green test results, decompensated liver function, jaundice, performance status, age, or the patients rejected it, even though the patients were satisfied with those conditions, TACE was considered the primary treatment.]

2) "The first paragraph of discussion should be the summary of findings."

→ Following the reviewer's advice, we have revised the first paragraph and eliminated the redundancies.

(3) ***Reviewed by 01588404***

1) "The authors have not mentioned the reason for opting for TACE versus resection in these patients."

→ We gave priority to surgical treatment and then considered other curative treatments, e.g. RFA. When curative treatments were difficult, it, even though the patients were satisfied with those conditions, TACE was considered the primary treatment. We have described the reasons on the "Subject" part

→ Many enrolled patients in this study had child A's liver function or 3cm and less (cancer size) or were solitary patients because only those patients (n = 134) who showed complete response were included and because those patients who had large and multiple cancers often continued to show incomplete response after all. A comparative analysis of the patients who showed complete response versus those who did not, liver functions, cancer counts and cancer sizes influenced the rate of achieving CR, which is beyond the scope of the given topic and thus not mentioned in this article.

2) "The authors should also report if there was any difference in recurrence rates after 2nd CR(early and late; numbers) for patients with early or late recurrence after 1st CR."

→ We have described in the "Effects of TACE on local recurrence area" part of the Result section that "no statistically significant difference was found between the 1st CR and 2nd CR and that late local recurrence was observed more often in the 2nd CR". Likewise, we have sub-divided all the cases into early/late recurrence in Figure 2.

3) "The authors have not mentioned any data regarding distant intra-hepatic recurrence in any of the 134 / 117 patients with CR."

→ We are grateful for the comment. We have drawn the graph in Figure 5 to compare the cumulative distant intra-hepatic recurrence using a log-rank test, and briefly described it in the "Result" section. We have found no statistically significant difference between the early and late local recurrence groups.

4) "The study had low rates of combination therapy especially after recurrence or in patients with 2nd recurrence. The second recurrence rate and higher CR after 1st recurrence might have been achieved in more patients if additional modalities were combined with TACE as the authors have themselves mentioned in the discussion."

→ We are grateful for the good comment. Certainly, had we administered a combination therapy for the 2nd recurrence lesion, the percentage of patients reaching CR would have increased. Yet, we found it challenging for many of our embolization patients to undergo RFA or surgery due to liver functions as well as the location and number of cancers. In this respect, it seems to be a limitation of this study that not many patients could opt for other treatments for the 2nd recurrence lesions. Although the present study was intended to observe the outcomes of other therapies as well, it was hard to make a conclusion as few patients were eligible for different treatments. Still, treatment outcomes were good with no recurrence being observed.

As early recurrence would reduce the treatment effects of TACE, it seems necessary to make efforts to extend the indications rather than strict criteria (e.g. in case a compact uptake occurs in a lesion treated in the past, RFA or wedge resection is applied to early local recurrence lesions only despite tumor number is many, or when TACE and RFA are similar in terms of risks and benefits, RFA should be considered first for re-treatment of early local recurrence lesions). Further studies are needed on the outcomes of this approach. Besides, Nexava has not been used in Korea until recent years because it is high-priced and uncovered by health insurance.

Nonetheless, as some studies have reported the combined TACE + Nexava treatment proved effective, it would be good practice to apply the combined treatment at least to those patients highly prone to early local recurrence. The present findings warrant more scrupulous research into the outcomes of different treatments applied to a larger sample of patients.

(4) Reviewed by 02527494

1) "Although the authors analyze the risk factors involved in early local recurrence after TACE, it is desirable to also present the risk factors associated with late recurrence after TACE."

→ The univariate analysis of risk factors for late local recurrence found no significant result, which

seems attributable to the small number of patients (19) who developed late local recurrence.

→ Univariate analysis of factors significantly predictive of late local recurrence after achieving complete response (in our study)

Variable	Univariate analysis		
	OR	95% CI	*P* value
Age (≥65 years)	0.884	0.298-2.619	0.824
Sex (female)	1.469	0.451-4.784	0.547
Tumor number, multiple	1.469	0.451-4.784	0.524
Tumor size(cm)			
2–5	1.736	0.572-5.266	0.330
>5	1.042	0.095-11.472	0.973
Child-Pugh score (≥8)	2.588	0.337-19.872	0.360
Decompensated LC	0.718	0.231-2.232	0.567
Gelfoam or PVA use	0.476	0.119-1.911	0.357
Bilirubin (>2.0 mg/dL)	2.500	0.148-42.160	0.525
Albumin (<3.5 mg/dL)	3.753	0.958-14.706	0.058
Ascites (present)	0.609	0.187-1.990	0.412
Post-CR AFP (>20 ng/mL)	0.643	0.155-2.663	0.542
Lipiodol uptake(non-compact)	2.687	0.349-20.716	0.343
TACE number to CR (≥2)	0.655	0.123-3.487	0.620

2) "This study includes 134 HCC patients, predominantly those with HBV (73, 54.5%). Recently, Yu SJ et al. demonstrated a high HBV viral load to be associated with the overall survival and a rapid disease progression in HCC patients after TACE (Yu SJ et al. Radiology 2013; 267: 638-647). Therefore, it is preferable to incorporate the viral status, such as the presence of viral infection, the HBV viral load and the types of anti-viral therapy that were administrated , into the variables when performing either a univariate or multivariate analysis with regard to the risk factors associated with early local recurrence after TACE. Such additional findings would improve the current work."

→ We thank the reviewer for the advice on good articles concerning HBV DNA levels. We analyzed pre- and post-treatment viral loads separately at cut-off levels of 1(2000 IU) and 2(20000 IU), respectively, with no significant results. We have perused an article that the reviewer cited as an example (Yu SJ et al. Radiology 2013; 267: 638-647). The patients enrolled in their study had no history of using anti-viral agents. In the present study, by contrast, many patients used anti-viral agents before diagnosis. Also, the history of treatment using anti-viral agents did not show any statistically significant results within the first month of treatment.

→Analysis about the use of antiviral agent, HBV viral load(in our study)

Variable	Univariate analysis		
	OR	95% CI	*P* value
Use of Anti-viral agent	1.632	0.749-3.577	0.218
Pre-treatment HBV viral load (≥2000 IU/mL)	1.432	0.475-4.319	0.524
Pre-treatment HBV viral load (≥20000 IU/mL)	1.642	0.588-4.585	0.344

Pre-CR HBV viral load (≥2000 IU/mL)	1.273	0.412-3.932	0.675
Pre-CR HBV viral load (≥20000 IU/mL)	1.333	0.487-3.649	0.575

3) "Kinugasa et al. suggested the lipiodol uptake after TACE to be associated with local recurrence after TACE (Kinugasa et al. J Gastroenterol. 2012; 47: 421-426). Therefore, it is preferable to include the lipiodol uptake in the variables when performing either a univariate or multivariate analysis with regard to the risk factors associated with early local recurrence after TACE. These findings would also improve the current work."

→ We are grateful for the comment. We have reinvestigated the part related to Lipiodol uptake. Kinugasa's article the reviewer mentioned seems to have focused on the early stage HCC (no more than 3 and 3cm) only. Based on the same criteria, none of the 15 patients of 5cm and above met the compact uptake in this article. Therefore, we considered the 75% uptake&200HU (Stefanini et al. *Cancer* 1995; 75(10): 2427-2434) applicable criteria to account for the results in this study.

4) "Generally, the Discussion section part is redundant in several areas. Especially, the Discussion from line 40-48 "Moreover, early recurrence lesions ~", this information should be described in the Results section. In the same manner, the Discussion section from line 85-92 " In this study, hepatic failure was ~" should be moved to the Methods section, the Discussion section from line 98-102 " Although it was not mentioned in the results,~" should be mentioned in the Results section. Moreover, because the authors mainly intend to focus on the phenomenon of local recurrence after TACE, the descriptions regarding complications after TACE should thus be minimized. Finally, we believe that the description regarding the occurrence of liver abscesses after TACE is unnecessary."

→ Considering that investigating all CR patients and their adverse effects would be meaningful, we inserted not just early local recurrence but also adverse effects in the discussion. Notably, as liver abscess or hepatic failure is a fatal adverse effect, we paid extra attention to reviewing. However, as the reviewer has pointed out, discussing both aspects is likely to lead to verbosity, possibly straying tangentially from the point. Although we summarized the adverse effects in the discussion, it would be better to exclude the summary of adverse effects. There would be no harm in effacing the text on adverse effects from the discussion section as it is elucidated in the "Complications" part in the "Result" section.

→ the Discussion from line 40-48 "Moreover, early recurrence lesions ~", this information was moved in the Results section.

→ the Discussion section from line 85-92 " In this study, hepatic failure was ~" was moved to the Methods section

→ the Discussion section from line 98-102 " Although it was not mentioned in the results,~" was removed in this article

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

Byung Seok Lee, MD, PhD, corresponding author
Division of Gastroenterology,
Department of Internal Medicine,
Chungnam National University College
282 Munwha-ro, Jung-gu
Daejeon 301-721, South Korea
Fax: +82-42-254-4553
E-mail: gie001@cnuh.co.kr

Woo Sun Rou, MD, first author
Division of Gastroenterology,
Department of Internal Medicine,
Chungnam National University College
282 Munwha-ro, Jung-gu
Daejeon 301-721, South Korea
E-mail: woosuni0912@hanmail.net